REMARKS

The Applicants respectfully request entry of the amendments set forth above and reconsideration and withdrawal of the restriction requirement, objections, and the claim rejections in view of the amendments and the following remarks.

Restriction Requirement

Applicants maintain their traversal of the restriction requirement as set forth in the previous office action response and respectfully request reconsideration and withdrawal of the restriction requirement.

Claim Objections

The Examiner objected to claims 150-155 and 157-161 under 37 CFR 1.75(c) to the extent of elements (d)-(f) on the ground that they are multiple dependent. Applicants respectfully submit that 37 CFR 1.75(c) does not form a proper basis for the objection because it is silent as to claims in which one or more elements is dependent on more than one element of the same claim. However, in the interests of furthering prosecution, Applicants have amended claim 150 by dividing prior element (c) into elements (c) and (c'), thereby obviating the objection, and have added claim 163. Withdrawal of the objection is respectfully requested.

Priority

Applicants note the Examiner's comments with respect to priority and reserve the right to address the issue again more fully at a later date in any forum. (In fact, the remarks below pertaining to written description support may be relevant to priority.) As set forth below, the claims are patentable over the cited art irrespective of which date the examiner recognizes.

Rejections under 35 U.S.C. 112 – written description

Claims 121-135, 137-140, 144-145, 150-155 and 157-161 stand rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. The Examiner

states that the claims differ substantially from those originally filed in the specification and points to two areas where support is allegedly lacking. Specifically, the Examiner asserts that the specification lacks support for the recitation of a "fibrous polymer" and for the phrase "comprising a fragment thereof".

The phrase "fibrous polymer" is fully supported by the specification as explained in the previous office action response. However, in the interests of furthering prosecution at this time, Applicants have amended claims 139 and 140 to recite a "polymer" rather than a "fibrous polymer".

The phrase "comprising a fragment thereof" is fully supported by the instant specification. The Examiner's attention is respectfully directed to the specification at paragraph 19 (p. 7, lines 10-14), stating that, "Exemplary SCHAG amino acid sequences include sequences of any naturally occurring protein that has the ability to aggregate into amyloid-type ordered aggregates under physiological conditions, such as inside of a cell. In one preferred embodiment, the SCHAG amino acid sequence includes the sequences of only that portion of the protein responsible for the aggregation behavior." The phrase "portion of the protein responsible for the aggregation behavior" clearly shows that Applicants had possession of the concept of a polypeptide comprising a "fragment" of a SCHAG amino acid sequence. The quoted passage in no way excludes SCHAG amino acid sequences that contain other portions of the relevant protein in addition to the portion of the protein responsible for the aggregation behavior. The specification further recites that, "Many such sequences have been identified in humans and other animals, including...prion protein and *fragments thereof*" (emphasis added). SEQ ID NO: 2, recited in the instant claims, represents the amino acid sequence of Sup35, a yeast prion protein, as described in the specification in paragraph 27 (p. 10, lines 17-18). Furthermore, original claim 11 recites a polynucleotide...wherein the at least one prion-aggregation domain comprises an amino acid selected from the group consisting of SEQ ID NOs: 2,...and prion aggregation domain *fragments thereof*." (emphasis added). Thus, the specification as filed clearly supports the recitation of "comprising a fragment thereof", both specifically with respect to fragments of SEQ ID NO: 2 and in general with respect to other SCHAG amino acid sequences.

The above remarks fully address the written description rejections set forth in paragraph 10 of the Office action. If the Examiner maintains the portion of the written description rejection set forth in section 10 of the Office Action, Applicants respectfully request clarification of which claims and which particular portions thereof are being rejected

and why the passages from the specification cited above fail to provide sufficient support, in order that Applicants can specifically address the rejection.

Claims 121-135, 137-140, 144-145, 150-155 and 157-161 also stand rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. In summary, the Examiner states that the claims "encompass various fragments, portions, and aggregates that are of nearly unlimited structural breadth" while "the specification is limited to experimentation with only particular Sup35/URE2 variants" and their analysis, which "does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera". The Examiner therefore maintains that Applicants did not have possession of the invention (Office Action, p. 13). Applicants respectfully traverse the rejection for each of the following reasons:

First, Applicants submit that the Examiner exaggerates the structural breadth permitted by the instant claims. The Examiner states that the disclosure and analysis of Sup35/URE3 variants does not support the scope of the "claimed genus", which "encompasses a substantial variety of subgenera". It is not clear whether the Examiner's reference to "the claimed genus" refers to a genus related to SEQ ID NO: 2, or whether the Examiner is instead referring to a broader genus of SCHAG amino acid sequences as described on pp. 6-12, of which the polypeptides of the instant claims are a subgenus. The Examiner alludes to the "multiple amino acid compositions and various aggregate structures as contemplated throughout pp. 6-12 of the specification" but does not explain how the scope of the subject matter on pp. 6-12 is relevant to the rejection of the instant claims.

As a result of the election of species required by a previous examiner in the restriction requirement issued on October 2, 2001, claims under examination in the Office action relate to polypeptides that are fragments or variants of SEQ ID NO: 2, polypeptides having specified degrees of identity with such polypeptides, and ordered aggregates comprising such polypeptides. The subject matter described on pp. 6-12, which discloses a variety of SCHAG amino acid sequences such as amyloid β sequences, immunoglobulin light chain fragments, serum amyloid A sequences, etc. (see p. 7, lines 10-31), is not all recited in the currently examined claims, and embodiments of the invention related to the sequences referred to therein (other than SEQ ID NO: 2) are not under examination until such time as at least one of the instant claims referring to SEQ ID NO: 2 is found allowable. To the extent that the Examiner is rejecting the instant claims based on the premise that they encompass subject matter contemplated by pp. 6-12 but not in fact recited in the claims, Applicants respectfully

request withdrawal of the rejection. Applicants submit, however, that the remarks below addressing the pending claims that recite SEQ ID NO: 2, would also apply to claims relating to other sequences, which would be under examination once subject matter related to SEQ ID NO: 2 is found allowable, thus supporting the generic claims as relevant to other sequences as well.

Rather than being "nearly inclusive of any polypeptide" as asserted by the Examiner (Office Action, p. 15), the pending claims are limited in the scope of sequences encompassed. For purposes of this discussion, Applicants will focus on claim 150 as being representative of the issues raised by the Examiner. Element (e) of claim 150 (e) has been amended to recite sequence variants that self-coalesce into ordered aggregates. Support for the specific variants recited in the claims is found in paragraph 27 (p. 11, lines 2-19), which indicates that the invention contemplates "sequences differing from the native sequences by the addition, deletion, or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acids", and "polypeptides that are at least about 99%, at least about 98%, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, or at least about 70% identical to one of (the) SCHAG amino acid sequences... but which retain the properties of prion-aggregation domains."

Element (c) of claim 150 recites "fragments of (a) that self coalesce into ordered aggregates", where "(a)" is "amino acids 2-253 of SEQ ID NO: 2". Element (c') of claim 150 recites "fragments of (b) that self coalesce into ordered aggregates", where (b)" is "amino acids 2-113 of SEQ ID NO: 2". The complete set of possible fragments of SEQ ID NO: 2 is limited in number and sequence identity. Each fragment of amino acids 2-253 or 2-113 of SEQ ID NO: 2, including those that self-coalesce into ordered aggregates, could be envisioned based on SEQ ID NO: 2. Each fragment would extend from any first amino acid within amino acids 2-253 or 2-113 of SEQ ID NO: 2 to any second amino acid within amino acids 2-253 or 2-113 of SEQ ID NO: 2. As already noted, the claims pertain to those fragments that self-coalesce into ordered aggregates.

Element (d) of claim 150 recites amino acid sequences that are at least 70% identical to the amino acid sequences of (a), (b), (c), or (c') and that self-coalesce into ordered aggregates. The complete set of sequences at least 70% identical to the amino acid sequences of (a), (b), (c), or (c') could readily be envisioned. Methodology for performing sequence alignments and determining percent sequence identity was well known in the art as of the filing date of the application. The Applicants also have provided extensive evidence of the

ability to retain the coalescing behavior with sequence variation, and provided guidance as to types of variation that are particularly supportive of coalescing behavior.

Element (e) of claim 150 recites amino acid sequence variants of the sequences of (a), (b), (c), or (c'), wherein the variations consists of addition, deletion, or substitution of 1-20 amino acids and that self-coalesce into ordered aggregates. Each such sequence could be obtained by making up to 20 amino acid modifications (addition, deletion, or substitution) to the relevant portion of SEQ ID NO: 2 or a fragment thereof. Each such variant could readily be envisioned and hence the written description requirement is met for this element. (Claim 150, as amended, no longer recites amino acid sequences that are variants of sequences that are at least 70% identical to the sequences of (a), (b), (c), or (c').) To the extent the rejection of the instant claims was based on the inclusion of such variants, Applicants respectfully request withdrawal of the rejection.

Element (f) of claim 150 recites sequence variants of (a), (b), (c), or (c'), wherein sequence variations from (a)-(c') consist of insertions or one or more sequences selected from the group consisting of: PQGGYQQYN (SEQ ID NO: 10) and variants of SEQ ID NO: 10 wherein one or two residues have been added, deleted, or substituted. Applicants submit that, since the sequences of (a), (b), (c), or (c') are adequately described, as discussed above, sequences that differ from (a), (b), (c), or (c') by insertions of one or more sequences selected from the group consisting of: PQGGYQQYN (SEQ ID NO: 10) and variants of SEQ ID NO: 10 wherein one or two residues have been added, deleted, or substituted are also adequately described. The application contains evidence of the effect of such sequences on coalescing activity.

It is not necessary to provide an exhaustive list of fragments and variants of SEQ ID NO: 2 in order to comply with the written description requirement, and one of skill in the art could readily envision each sequence based on the language of the claims and the knowledge of one of skill in the art. As discussed in the specification and further discussed below, fragments and variants that self-coalesce into ordered aggregates can be readily distinguished from those that do not. Applicants have provided the sequences of a number of polypeptides falling within the scope of the claims that self-coalesce into ordered aggregates.

Second, Applicants submit that the holdings in *Lilly* and in *Fiers* cannot properly be applied to reject the instant claims and in fact support their patentability. In *Lilly*, the CAFC invalidated "species claims" requiring human insulin-encoding cDNA, and "genus claims" requiring vertebrate or mammalian insulin-encoding cDNAs, where the patent applicant had

disclosed the sequence of only rat cDNA and a process for obtaining additional cDNAs. The CAFC noted that, "A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein.". *In re* Lilly, 119 F.3d 1559 at 1567 (Fed. Cir. 1997). Thus, sequence information was needed to distinguish the specifically claimed cDNA, i.e., *human* cDNA, from other cDNAs that encode human insulin. In contrast, Applicants are not presently claiming *a specific, isolated natural nucleic acid or protein of as yet unidentified sequence* based solely on function and an identifying name, as in the case of the human insulin-encoding cDNA claimed in *Lilly*. Applicants' pending claims are to polypeptides that comprise a fragment or variant *of a known sequence*, i.e., amino acids 2-253 or 2-113 of SEQ ID NO: 2, wherein claimed polypeptides fulfill structural requirements that allow the polypeptide to interact with other identical or highly similar polypeptides so as to form higher ordered aggregates. As noted above, the sequence of each fragment or variant of SEQ ID NO: 2 recited in the claims would be evident to one of skill in the art. The same would be true for any of the other polypeptides disclosed in the specification as comprising SCHAG sequences and included in the generic claims. In *Lilly*, the CAFC stated, "The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, *there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics...*" *Id.* (emphasis added). In contrast, the instant specification provides abundant information pertaining to the sequence of the claimed polypeptides and also provides structural and physical characteristics of the claimed polymers. Thus the CAFC's holding in *Lilly* with respect to the claim to human cDNA does not support a rejection of the instant claims.

Furthermore, Applicants submit that *Lilly's* holdings with respect to claims involving cDNA encoding vertebrate or mammalian insulin does not support a rejection of the instant claims. Applicants are not presently claiming cDNAs at all, and are not claiming a genus while describing only a single species as in the case of the vertebrate and mammalian cDNAs claimed in *Lilly*. As described in Examples 3 and 10, Applicants generated a large number of polypeptides falling within the scope of the instant claims and employed two different methods to characterize formation of higher order structures from a number of different polypeptides. The polypeptides described in Examples 3 and 10 constitute a sufficient

number of species to provide adequate description of the pending claims in accordance with the holding in *Lilly*, acknowledged by the Examiner, that "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs...falling within the scope of the genus." Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art" *Angstadt*, 537 F.2d 498, 502-03 (CCPA 1976).

With respect to generic claims that encompass polypeptides other than segments, fragments, or variants of SEQ ID NO: 2, Applicants have previously drawn the Examiner's attention to the non-limiting list of SCHAG sequences on p. 7 of the specification, which recites: amyloid β protein (residues 1-40, 1-41, 1-42, or 1-43); ...immunoglobulin light chain fragments ...; serum amyloid A fragments...; transthyretin and transthyretin fragments...; cystatin C fragments...; β2-microglobulin...; apolipoprotein A-1 fragments...; a 71 amino acid fragment of gelsolin...; islet amyloid polypeptide fragments...; calcitonin fragments...; prion protein and fragments thereof...; atrial natriuretic factor...; lysozyme and lysozyme fragments...; insulin...; and fibrinogen fragments." These sequences are well known in the art, and accordingly it is not necessary for Applicants to recite the sequences themselves in the specification as it is settled that, "[a] patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F. 2d 1524, 1534 (Fed. Cir.1987). Furthermore, the specification describes identification of novel yeast prion Rnq1 based on sequence composition and shows that a portion of the Rnq1 sequence having similar overall amino acid composition to Sup35 and URE2, but differing in primary amino acid sequence possesses ability to self-coalesce into higher ordered aggregates (see Example 6).

The specification also provides guidance as to how naturally occurring sequences such as the segments of SEQ ID NO: 2 recited in the instant claims, or the sequences named above, could be modified to produce synthetic SCHAG sequences, such as by making conservative substitutions (p. 8, lines 12-14), adding or substituting polar residues such as glutamine, asparagines, serine, and tyrosine into naturally occurring sequences (p. 8, lines 29-31), duplication of repeat sequences found in naturally occurring SCHAG sequences (p. 9, lines 1-3), etc. As noted in the previous office action response, the specification teaches that the percentage of polar residues (particularly asparagine and glutamine) is important for fiber forming properties of a polypeptide. The specification contains repeated guidance that SCHAG peptides preferably are rich in polar, uncharged residues (especially asparagines (N) and glutamine (Q), but also serine and tyrosine). For example, whereas an average globular

protein may have a Q + N amino acid content of about 8%, prion proteins such as those described in the application typically have a Q + N content in excess of 30%. [See Exhibit B to the amendment filed on July 13, 2004, providing amino acid content of Sup35 and Ure2, broken down by domains. The N region of each molecule is the polar-residue rich SCHAG/prion domain.] At the same time, a typical globular protein will have approximately 26% charged residues (K,R,E,D), whereas in the typical prion domain, the K+R+E+D content is less than about 12%.

It is incorrect to assert that "the specification is limited to experimentation with only particular Sup35/URE2 variants and analysis via spectroscopy and electron micrographs" (Office Action, p. 13). As noted above, in addition to Sup35/URE2, the specification describes identification of novel yeast prion Rnq1 and shows that a portion of the Rnq1 sequence possesses ability to self-coalesce into higher ordered aggregates (see Example 6). Therefore, to the extent that the rejection is based on the premise that the specification is limited to experimentation with particular Sup35/URE2 variants, Applicants respectfully submit that it should be withdrawn.

Even if the specification were limited to experimentation with only particular Sup35/URE2 variants, the Examiner would not be entitled to conclude, on that basis, that written description is lacking. Variants of Sup35 are recited in the claims currently under examination. Applicants described and performed experiments with a number of Sup35 variants. Applicants used at least two methods to characterize formation of higher ordered structures. The law does not require Applicants to perform experiments with every sequence that falls within the scope of their claims or to utilize more than two methods of analysis in order to meet either the written description or enablement requirement. Rather than being inadequate, the experiments and methods used provide additional supporting evidence that Applicants had possession of the claimed subject matter since they demonstrate that a variety of the claimed polypeptides have been made and self-coalesce into ordered aggregates. Furthermore, the two methods disclosed are sufficient and appropriate to allow one of ordinary skill in the art to determine, using no more than routine experimentation, whether any particular polypeptide, including but not limited to, a fragment or variant of amino acids 2-253 or 2-113 of SEQ ID NO: 2 will self-coalesce to form fibers.

Applicants note the Examiner's comments regarding claims 130, 131, and 134 (Office Action, p. 17). Applicants have amended claims 130 and 131 to clarify the functional requirements recited therein. In Example 9, Applicants describe performing electron

microscopy, evaluating fiber assembly kinetics using Congo red staining, and obtaining circular dichroism measurements on higher ordered structures formed by self-coalescence of a polypeptide comprising amino acids 2 to 253 of SEQ ID NO: 2. Therefore, Applicants submit that it is clear they were in possession of this descriptive data as evidenced, e.g., by Table 1. The data obtained from these various techniques represents "physical properties" of the claimed polypeptides. As noted by the Examiner, physical properties provide one means of providing an adequate written description of a biological macromolecule. (Office Action, p. 14, citing *Fiers v. Revel*). Applicants further note that, "there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). There are many ways to describe a molecule other than by its sequence. MPEP 2163 describes several such methods including isolectric points, comparison of enzyme activities, antibody cross-reactvity. Applicants submit that the methods they employed to characterize and describe the claimed polypeptides are equally acceptable since, e.g., they distinguish the claimed polypeptides from polypeptides that do not self-coalesce to form fibers.

The specification clearly uses "ordered aggregate" and "higher ordered aggregate" interchangeably. The Examiner has not presented any evidence to suggest that one of skill in the art would find the terms "fiber morphology" unclear. Applicants note that the structure of amyloid fibers has been recognized in the art for many years, and the very articles cited by the examiner in the Office action demonstrate acceptance in the art and understanding of these terms by the workers in the field of the invention. The Examiner has presented no evidence that one of skill in the art would not recognize what is meant by an ordered aggregate having a fiber morphology. To the contrary, the Examiner cited numerous documents of record (see, e.g., p. 15 of Office action) that show that people in the field are quite comfortable with recognizing the structures formed by polypeptides of the invention.[1] The application describes characteristics of the aggregates and analytical tools used in the field to identify them. As the audience for the application is the workers of ordinary skill in the field, nothing further could be required.

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[1] The Applicants also note that the description in the literature of some conditions under which fibers allegedly do not form (or do not form as readily) in no way diminishes the descriptive teachings in the application of conditions under which the polypeptides do self-coalesce into higher order aggregates.

The specification thus (i) repeatedly teaches that the amino acid *composition* of a polypeptide, rather than the sequence per se, is an important structural factor for conferring SCHAG properties; (ii) discloses a multitude of specific polypeptides that self-coalesce to form higher ordered structures (see list recited above); (iii) provides guidance regarding the nature of modifications that may be made to such polypeptides while preserving their ability to self-coalesce to form higher ordered aggregates; and (iv) demonstrates that additional polypeptides having SCHAG properties can be identified based on sequence composition.

The holdings in *Lilly* in fact support patentability of the claims. As noted by the Examiner, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Applicants have disclosed a sufficient number of polypeptide sequences having SCHAG properties to support generic claims. As noted above, Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art". *Angstadt, supra.* See also MPEP 2163, noting that, "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." In addition, Applicants submit that their disclosure of a large number of naturally SCHAG sequences of known sequence composition, taken together with Applicants' description of the importance of amino acid composition for conferring SCHAG properties, adequately describes structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Applicants note the Examiner's comments that the references in subparagraph D of the previous office action response are post filing date and thus cannot be used to describe Applicants' claims. These references were not cited to provide description or enablement that is missing from the instant specification or to describe what was known in the art as of the filing date. The references clearly show that the importance of amino acid composition, *as taught in the application by Applicants*, has been confirmed by additional experimental evidence obtained by others. The references confirm that, in the technology area of the instantly claimed invention, the structural features common to the genus and that correlate with the function of self-assembly to form higher ordered aggregates, lie in the overall amino acid composition of the species, rather than in their specific primary sequences. The cited references thus confirm that the specification *as filed* adequately describes and enables the

claims. In summary, the specification satisfies both of the two approaches set forth in *Lilly* by which a genus of biomolecule sequences can be adequately described.

Fourth, a conclusion that the instant claims meet the written description requirement flows directly from the holding in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 77 U.S.P.Q. 2d 1161 (Fed. Cir. 2005). In that case, the Federal Circuit addressed the relevance of *Lilly* and *Fiers* to claims to a genus of polypeptides, where the polypeptides are described at least in part on the basis of function. The case demonstrates that, contrary to the Examiner's contention on p. 15 of the Office Action, "the ability of making and testing", together with at least one representative embodiment can sufficiently describe a genus of sequences.

In *Invitrogen*, the CAFC held that claim 1 of Invitrogen's U.S. Pat. No. 6,063,608, drawn to a genus of polypeptides described by function (reverse transcriptase (RT) activity and reduced RNase H activity), is valid. Claim 1 reads as follows:

> An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, *Neurospora*, *Drosophila*, primates and rodents.

The '608 patent teaches that "RT genes having DNA polymerase activity and substantially no RNase H activity may be obtained by deletion of deoxyribonucleotides at the 3' end of the gene which encode the portion of the polypeptide having RNase H activity" (col. 10, lines 57-62). However, claim 1 does not limit the claimed genus to polypeptides having this modification. The specification does not describe precisely how much of the gene may be deleted while retaining DNA polymerase activity and which portions must be retained in order to preserve the functions recited in the claims. Sequences of homologous genes encoding RT from a number of sources were known in the art when the '608 application was filed. However, claim 1 does not limit the claimed sequences to known sequences. The '608 patent provides only one sequence of a polypeptide falling within the scope of claim 1 and implicitly acknowledges that the skilled artisan would need to test a modified RT in order to determine whether it possessed DNA polymerase activity and/or RNase H activity (see col. 11, lines 3-9 of the '608 patent, referring to methods that one of skill in the art could use to test a modified RT for these activities) polypeptide in order to determine whether it falls

within the scope of claim 1. The CAFC recognized that the '608 patent "claims a compound (the polypeptide or genetically engineered RT) in terms of biological functions (DNA polymerase and RNase H activity)". *Invitrogen*, 429 F.3d 1052 at 1072-1073; 77 USPQ 2d 1161 at 1174 (Fed. Cir. 2005).

Clontech asserted that claims in the '608 patent that did not recite sequences were invalid based on the holdings of *Lilly* and *Fiers*. The CAFC rejected this argument, stating that, "Clontech's appeal to *Eli Lilly* and *Fiers* is misplaced. In those cases, the patent specifications at issue did not identify the sequence (structure) of any embodiment of DNA claimed therein. ... In contrast, the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features - DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient."

In summary, the '608 patent claims a genus of polypeptides based on functional characteristics and a representative embodiment. The CAFC held that the '608 specification met the written description requirement because, unlike the patents at issue in *Lilly* and *Fiers*, the '608 patent *provided the sequence of a representative embodiment, methods for obtaining additional embodiments, and methods by which one of ordinary skill in the art could determine whether any particular polypeptide possessed the claimed functional activities*. As noted above, the instant patent application provides sequences of multiple representative embodiments falling within the scope of the claims. The instant specification also provides methods for obtaining additional embodiments and methods for determining whether any particular polypeptide meets the functional requirements of the claims. Applicants submit that the holding in *Invitrogen* clarifies that *Lilly* and *Fiers* should not be used to reject claims to a genus of nucleic acids or polypeptides, where the claims recite a function and the specification provides the sequence of a representative embodiment, methods to obtain additional embodiments, and methods to test those embodiments for the function, as does the instant specification. Applicants submit that, based on the holdings in *Invitrogen*, the instant claims meet the written description requirement.

For each of the reasons above, Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. 112 – enabling disclosure

Claims 121-135, 137-140, 144-145, 150-155 and 157-161 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. It is settled that the Examiner has the "initial burden of setting forth a reasonable explanation as to why the scope of protection provided by [the claims] is not adequately enabled by the description of the invention provided in the specification." *In re Wright,* 999 F.2d 1557 (Fed. Cir. 1993). Applicants respectfully submit that for each of the following reasons, the Examiner has not established a *prima facie* case that enablement is lacking.

Firstly, the Examiner has provided no evidence that one of skill in the art could not make and use the invention as claimed. The specification provides numerous sequences that self-coalesce to form higher ordered aggregates and shows data indicating that the sequences do self-coalesce to form higher ordered aggregates. As noted above, the specification teaches a variety of modifications that could be made to known SCHAG polypeptides. The Examiner has not provided any evidence to suggest that conservative substitutions, additions or deletions within the bounds recited in the claims, would fail to result in polypeptides that self-coalesce. Furthermore, the specification clearly describes how to identify additional polypeptides that self-coalesce to form higher ordered aggregates without undue experimentation (e.g., Example 6). References cited in subparagraph D of the previous office action response show that a wide range of polypeptides with sequences rich in polar residues such as asparagine and glutamine are able to self-coalesce to form higher ordered aggregates, thus confirming the enabling teachings and guidance of the application. As will be evident from the discussion above, the scope of the claims is not "inclusive of nearly any amino acid sequence under any condition" as stated by the Examiner (Office Action, p. 21).

The Examiner states that, "A teaching of a single experimental condition for a single peptide does not approach enabling all conditions under which all proteins form suitable nanotechnology products of particular form." (Office Action, p. 22). Applicants are not required to enable all conditions under which all proteins form suitable nanotechnology products of particular form. Applicants are only required to enable the claimed invention, which does not encompass all proteins and does not require the ability to self-coalesce to form higher ordered aggregates under all conditions. Indeed, the CAFC has explicitly stated, "Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would

not include improved modes of practicing those inventions. Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain." *Invitrogen*, 429 F.3d 1052 at 1071 (Fed. Cir. 2005). As the claims pertain to polypeptide products, the enabling teaching of a single set of conditions in which the polypeptides can be used is sufficient to satisfy the statutory requirement.[2]

The specification teaches that, "the term "self-coalesces" refers to the property of the polypeptide to form ordered aggregates with polypeptides having an identical amino acid sequence *under appropriate conditions as taught herein*, and is not intended to imply that the coalescing will naturally occur under every concentration or every set of conditions." See specification at paragraph 18 (p. 6, lines 25-29). The specification teaches that physiological conditions, such as those found in a cell or in a solution mimicking the physiological salt concentrations found in cells, are appropriate conditions. See specification, e.g., at paragraph 19 (p. 7, lines 10-31). The claims are drawn to compositions. The law does not require that all possible conditions and processes will be appropriate to make a claimed composition in order for the composition to be adequately described. Neither are Applicants required to enable all possible ways of making the compositions. The claims do not require that any peptide amino acid sequence can be converted into a prion or prion-like structure as suggested by the Examiner (Office Action, p. 21).

Moreover, in order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d, 731 at 737 (Fed. Cir. 1988) and MPEP 2164.02). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra. Applicants submit that synthesizing any any particular polypeptide, maintaining it *in vitro* under conditions such as those taught in the specification, and applying the methods for assessing formation or ordered aggregates described in the specification is well within the skill in the art. As noted above, the specification provides considerable guidance as to appropriate modifications to retain self-coalescing properties. The Examiner has not shown any evidence of excessive

[2] The Examiner's emphasis (see office action at p. 21) that the claims are "in part directed to the secondary and tertiary structure" is not entirely understood and would seem to undermine the alleged basis for restricting the polypeptide claims from the ordered aggregate claims.

unpredictability associated with the practice of the instant claims and has acknowledged that variability in Sup35 sequence may exist without altering the ability to form prion-like molecules. (Office Action, p. 21). As already noted, the existence of literature that has characterized factors that affect coalescing in no way detracts from the fact that the application teaches conditions permissive of coalescing.

In addition, Applicants submit that the Examiner is applying an incorrect legal standard in stating that "experimentation is undue where there is not a predictable outcome" (Office Action, p. 21). Applicants are not aware of any requirement for a predictable outcome in the law or set forth in the MPEP. If the outcome of an experiment is predictable there is no need to perform an experiment. Clearly the legal standard for enablement permits experimentation where the outcome is not predictable. Furthermore, there is no basis in the law for the Examiner's suggestion that the specification must provide "information as to how much variation under any particular conditions are (*sic*) tolerable without loosing (*sic*) the ability to form such prion-like structures." Moreover, it is noted that the claims *do* set forth limitations on the sequence variability based on percent identity and number of permissible substitutions, deletions, and additions. See, e.g., independent claims 124, 127, 144, and 150.

Finally, and importantly, all of the evidence of record clearly and conclusively establishes that when a person makes variants within the scope of the genus defined by structural limitations in the claims and tests the variants, it is quite predictable that the person will succeed at making variants that have the desired aggregation properties. Just as in the *Wands* case, where not every monoclonal antibody that was made and tested would be expected to have the properties required by the *Wands* claims, there is no requirement under the law that the result for every peptide screened by predictable. Rather, expectation of successes without undue experimentation is reasonably predicted from the teachings in the application and the totality of evidence of record, and is judged by evaluating the entire synthesis/screening process. The Examiner has failed to identify a single reference or other evidence suggesting that when a person of ordinary skill sets out to design variants according to the teachings in the application, the person would require undue experimentation to succeed. The applicants, on the other hand, have provided abundant evidence that such efforts predictably result in successes.

In summary, for each of the above reasons Applicants submit that the instant claims meet the enablement requirement and respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. 112 - definiteness

Claims 126, 132-133, 150-155, and 157-161 stand rejected under 25 U.S.C. 112, second paragraph, as being indefinite. Claim 126 has been amended to recite an amino acid with a reactable side chain, for which antecedent basis exists in claim 124. Claims 132 and 133 have been amended to clarify the position of the amino acid with the reactable side chain. Claim 150 has been amended as discussed above, thereby obviating the alleged difficulty in determining structural limitations of elements (e) and (f).

The Examiner maintains that claims 150-155 and 157-161 are indefinite on the ground that the structural limitations of elements (e) and (f) cannot be determined. Applicants respectfully disagree. Element (e) has been amended to encompass only fragments that self-coalesce into ordered aggregates. Even if it was reasonable to interpret the "fragment" of element (e) as including molecules that consist of one or two amino acid residues, which Applicants do not concede, there is no evidence that such molecules would self-coalesce to form ordered aggregates as recited in claim 150. As discussed below, the Examiner is not entitled to conclude that any particular polypeptide or fragment possesses the ability to self-coalesce to form an ordered aggregate in the absence of evidence to this effect. In fact, the Articles cited by the Examiner throughout the Office action establish that people in the field of the invention are familiar with the type of aggregation described in the application and have no difficultly distinguishing it from other behaviors that do not satisfy the claims. Furthermore, even if molecules consisting of one or two amino acids were encompassed, this would not render the claim indefinite, simply broad. Element (f) recites SEQ ID NO: 10 (PQGGYQQYN) and variants of SEQ ID NO: 10 wherein one or two residues have been added, deleted, or substituted. SEQ ID NO: 10 and the recited variants are at least 7 amino acids long. Applicants submit that one of skill in the art can readily determine whether SEQ ID NO: 10 or a variant thereof is present in a polypeptide. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. 102

As explained in detail in the following paragraphs, all of the prior art rejections are based on improper construction of the claims, a misapplication of the law of inherency and anticipation, or both. The current claims specify that, to the extent the claimed polypeptide comprises a "fragment" (e.g., fragment of SEQ ID NO:2), *the fragment itself be one that self-*

coalesces to form higher ordered aggregates. In each of the rejections, the Examiner selects an amino acid, dipeptide, or tripeptide sequence and asserts that the small peptide meets the claim limitations. However, the Examiner fails to provide any reasoning or evidence that these di- and tri-peptides self coalesce into higher ordered aggregates, as that term is used in the application and understood in the field of the invention. In the absence of showing that the prior art satisfies these claim limitations, the rejections must be withdrawn.

Claims 121-123, 139, 144, 150-151 and 157-158 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wei, et al., *J. Biol. Chem.*, 273(19):11806-814, 1998 (hereinafter "Wei"). Claims 121-123 and 139 depend on claim 144, which reads as follows:

> A polypeptide comprising the SCHAG amino acid sequence of SEQ ID NO: 2, with the proviso that amino acid 184 of SEQ ID NO: 2 has been substituted for by a cysteine or glutamate, or comprising a fragment thereof that includes said substituted amino acid *and that self-coalesces to form higher ordered aggregates*.

The Examiner appears to maintain that since cystatin C includes a cysteine residue, and since the instant claims encompass polypeptides that comprise a fragment of SEQ ID NO: 2 containing a cysteine substitution, the presence of a cysteine residue in cystatin C means that cystatin C anticipates the claims. Applicants respectfully disagree. Applicants are not claiming every polypeptide that self-coalesces and that comprises *any* fragment of SEQ ID NO: 2. Applicants submit that the Examiner has overlooked the portion of claim 144 reciting the self-coalescing properties of the fragment (indicated in italics above). Even if it was reasonable to interpret the term "fragment" as including molecules consisting of a single amino acid, which Applicants do not concede, *there is no evidence to suggest that a single amino acid would possess self-coalescing properties recited in the claims*. The broadest reasonable interpretation of the claims is not an interpretation that ignores some of the claim limitations.

As pointed out in the previous office action response, the Examiner is not entitled to assume the self-coalescing properties recited in the claims in the absence of evidence. As summarized in MPEP 2112, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." (Emphasis in original) *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), *In re Oelrich*, 666 F.2d 578, 581-582, 212 USPQ 323, 326 CCPA 1981). Rather, "[t]o make or establish inherency, the extrinsic evidence 'must make clear

that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " (emphasis added) *In re Robertson*, 169 F.3d 743, 749, 49 49 USPQ2d 1949, 19502-51 (Fed. Cir. 1999). There is nothing in the specification and nothing in Wei to suggest that cysteine would possess the self-coalescing properties recited in the claims. The Examiner has not presented any evidence to suggest that cysteine would possess such properties. Therefore, Applicants submit that a cysteine residue is not "a fragment of SEQ ID NO: 2 that includes said substituted amino acid and that self-coalesces to form higher ordered aggregates." Accordingly, the presence of cysteine in cystatin C does not render the claimed polypeptides anticipated by cystatin C. (The examiner has failed to identify a larger, aggregate-forming polypeptide in Wei et al. that satisfies structural limitations of the claims.) Applicants further note that the Examiner has provided no evidence to support the statement that "All residues are exposed to the environment" in fibers formed by cystatin C. (Office Action, p. 24). For all of these reasons, Wei does not anticipate the claimed invention, and the Applicant's request withdrawal of the rejection.

Claims 121-123, 139, 144, 150-151 and 157-158 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kushnirov, et al., *Yeast*, 6:461-472, 1990. The Examiner notes that lysine 184 is present in the sequence context "TKE" in the Sup35 gene of *Saccharomyces cerevisiaie* and that substituting "E" for lysine 184 in "TKE" would result in "TEE", which is present in Sup35 of *Pichia pinus* as taught by Kushnirov. The Examiner concludes that *Pichia pinus* Sup35 anticipates the claims. Applicants respectfully disagree. Applicants are not claiming every polypeptide that self-coalesces and that comprises *any* fragment of SEQ ID NO: 2. Claim 144 specifies that the fragment itself self-coalesces to form higher ordered aggregates. (See also claim 150 parts c and c'). There is nothing in the specification or in Kushnirov to suggest that the sequence "TEE" would possess the self-coalescing properties recited in the claims. The Examiner has not presented any evidence to suggest that "TEE" would possess such properties. Applicants submit that the Examiner has failed to establish that the sequence "TEE" in Sup35 of *Pichia pinus* would possess the self-coalescing properties recited in the claims. Thus, even if the Examiner's interpretation of the term "fragment", as used in the instant claims, was reasonable, which Applicants do not concede, the presence of "TEE" in *Pichia pastoris* Sup35 does not render the claimed

SCHAG polypeptide anticipated by *Pichia pastoris* Sup35. The Examiner has not cited a larger peptide in Kushnirov that satisfies the structural limitations of the claims. Applicants therefore respectfully submit that Kushnirov does not anticipate the claimed invention and request withdrawal of the rejection.

Claims 150-151 and 157-158 are drawn to SCHAG polypeptides having at least one substituent attached thereto. Solely for purposes of clarity, claim 150 has been amended to clarify that the substituent is attached to a side chain of an amino acid in the polypeptide. Support for the amendment is found throughout the specification, e.g., in paragraph 60 (p. 25, lines 15-31). While Applicants do not concur with the Examiner's contentions regarding amino acid specific antibodies and light altering substituents, Applicants submit that the rejection is rendered moot for the reasons stated above. Withdrawal of the rejection is respectfully requested.

Claims 144-145, 139-140, 150-155, and 157-161 stand rejected under 35 U.S.C. 102(e) as being anticipated by Prusiner, et al., U.S. Pat. No. 6,277,970 (hereinafter "Prusiner"). The Examiner notes that residue 2 of SEQ ID NO: 2 is in the context of "MSD" and that substitution of "S" by "C" would result in "MCD". The Examiner notes that residue 184 of SEQ ID NO: 2 is in the context of "TKE" and that substitution of "K" by "E" would result in "TCE". The Examiner notes the presence of "CD" and "CE" in SEQ ID NO: 2 and 4 of Prusiner and concludes that these peptides anticipate the claims. Applicants respectfully disagree. Applicants are not claiming every polypeptide that self-coalesces and that comprises *any* fragment of SEQ ID NO: 2. As explained above, the claims specify a fragment that self-coalesces. There is nothing in the specification or in Prusiner to suggest that the sequences "CD" or "CE" would possess the self-coalescing properties recited in the claims. The Examiner has not presented any evidence to suggest that "CD" or "CE" would possess such properties. Applicants submit that the Examiner has failed to establish that the sequence "CD" or "CE" in SEQ ID NO: 2 or 4 of Prusiner would possess the self-coalescing properties recited in the claims. Thus, even if the Examiner's interpretation of the term "fragment", as used in the instant claims, was reasonable, which Applicants do not concede, the presence of the sequences "CD" or "CE" in SEQ ID NO: 2 and 4 of Prusiner does not render the claimed SCHAG polypeptide anticipated by SEQ ID NO: 2 or 4. Applicants therefore respectfully submit that Prusiner does not anticipate the claimed invention and request withdrawal of the rejection.

The Examiner states that claim 150 encompasses fragments regardless of self-coalescing activity. Applicants respectfully disagree. The elements of claim 150 that recite fragments all recite fragments that self-coalesce. To the extent that the rejection was based on the premise that claim 150 encompasses fragments regardless of self-coalescing activity, Applicants submit that it should be withdrawn for this reason in addition to the reasons stated above.

Claims 121-123, 139-140, 144-145, 150-155, and 157-161 stand rejected under 35 U.S.C. 102(e) as being anticipated by Glabe, et al., U.S. Pat. No. 6,600,017 (hereinafter "Glabe"). The Examiner notes that residue 2 of SEQ ID NO: 2 is in the context of "MSD" and that substitution of "S" by "C" would result in "MC" or "CD". The Examiner notes that residue 184 of SEQ ID NO: 2 is in the context of "TKE" and that substitution of "K" by "E" would result in "CE". The Examiner notes the presence of "MC", "CD" and "CE" in beta amyloid peptides taught by Glabe, following cysteine substitution and concludes that these peptides anticipates the claims. Applicants respectfully disagree. Applicants are not claiming every polypeptide that self-coalesces and that comprises *any* fragment of SEQ ID NO: 2. There is nothing in the specification or in Glabe to suggest that the sequences "MC", "CD" or "CE" would possess the self-coalescing properties recited in the claims. The Examiner has not presented any evidence to suggest that "MC", "CD", or "CE" would possess these properties. Applicants submit that the Examiner has failed to establish that the sequence "MC", "CD", or "CE" in the beta amyloid peptides of Glabe would possess the self-coalescing properties recited in the claims. Thus, even if the Examiner's interpretation of the term "fragment", as used in the instant claims, was reasonable, which Applicants do not concede, the presence of the sequences "MC", "CD" or "CE", in the beta amyloid peptides taught by Glabe does not render the claimed SCHAG polypeptide anticipated by the beta amyloid peptides. Applicants therefore respectfully submit that Glabe does not anticipate the claimed invention and request withdrawal of the rejection.

The Examiner states that claim 150 encompasses fragments regardless of self-coalescing activity. Applicants respectfully disagree. The elements of claim 150 that recite fragments all recite fragments that self-coalesce. To the extent that the rejection was based on the premise that the claim encompasses fragments regardless of self-coalescing activity, Applicants submit that it should be withdrawn for this reason in addition to the reasons stated above.

Claims 145, 139, 150-152, and 154 stand rejected under 35 U.S.C. 102(e) as being anticipated by Prusiner, et al., U.S. Pat. No. 5,962,669 (hereinafter "Prusiner2"). The Examiner notes that residue 2 of SEQ ID NO: 2 is in the context of "MSD" and that substitution of "S" by "C" would result in "MC". The Examiner notes that Prusiner2 teaches peptides that contain "MC" and that self-coalesce and concludes that these peptides anticipate the claims. Applicants respectfully disagree for the reasons set forth above in reference to Prusiner. Applicants are not claiming every polypeptide that self-coalesces and that comprises *any* fragment of SEQ ID NO: 2. There is nothing in the specification or in Prusiner2 to suggest that "MC" would possess the self-coalescing properties recited in the claims. The Examiner has not presented any evidence to suggest that "MC" would possess these properties. Applicants submit that the Examiner has failed to show that the sequence "MC" would possess the self-coalescing properties recited in the claims, as would be required for anticipation. Thus, even if the Examiner's interpretation of the term "fragment", as used in the instant claims, was reasonable, which Applicants do not concede, the presence of the sequence "MC" in the peptides taught by Prusiner2 does not render the claimed SCHAG polypeptide anticipated. Applicants therefore respectfully submit that Prusiner2 does not anticipate the claimed invention and request withdrawal of the rejection.

The Examiner states that claim 150 encompasses fragments regardless of self-coalescing activity. Applicants respectfully disagree. The elements of claim 150 that recite fragments all recite fragments that self-coalesce. To the extent that the rejection was based on the premise that the claim encompasses fragments regardless of self-coalescing activity, Applicants submit that it should be withdrawn for this reason in addition to the reasons stated above.

CONCLUSION

For the foregoing reasons Applicants respectfully request that the restriction requirement and rejections be withdrawn and that the claims be allowed. If this response requires any fee or a petition for extension of time that has not been filed herewith, then please consider this a request for such extension of time and charge any fees due to charge Marshall, Gerstein & Borun, LLP, deposit account number 13-2855, under matter number 30554/34978A.

Respectfully submitted,

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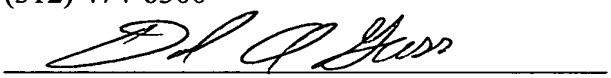
By: 

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